**Table**
Donor-recipient 8 HLA-allele match (N = 70 units)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | (N) |
|---|---|---|---|---|---|---|---|---|---|
| **6/6** | | | | | 25% | 25% | 25% | 25% | **4** |
| **5/6** | | | 5% | 19% | 26% | 35% | 16% | | **43** |
| **4/6** | | 13% | 26% | 26% | 30% | 4% | | | **23** |

**Conclusions:** Despite high-risk disease and grafts with a very high degree of donor-recipient HLA-allele mismatch, the low TRM and relapse rates after pediatric DCBT are striking, with either TBI-based or chemotherapy-only conditioning. Although young children could have adequate single-unit grafts, a significant percentage will not. Therefore, DCBT remains an important consideration, especially for children of ethnic minorities.

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### Ex Vivo T Cell Depleted HLA-Matched PBSCT with Post-Transplant Activated Donor-Derived NK Cell Infusions for High-Risk Acute Lymphoblastic Leukemia

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**Background:** Relapse is the primary cause of treatment failure following allogeneic HCT. Preclinical data demonstrates that large numbers of activated NK cells can be generated ex vivo using artificial APCs (aAPC), that these activated NK cells readily kill pediatric leukemia, and that activity is independent of KIR mismatch. The post-transplant period may be favorable for expansion and survival of adoptively transferred NK cells potentially providing an additional anti-leukemia effect.
**Methods:** We initiated a Phase I trial to assess safety and feasibility of administration of escalating doses of donor-derived activated NK cell infusions (NK-DLI) following myeloablative HLA-matched T-cell depleted PBSCT. Donors underwent apheresis for filgrastim mobilized PBSC. The product was T cell depleted and CD34/CD56 selected. The CD56+ fraction was cultured for 9–11 days with a K562 based aAPC expressing 4-1BBL and IL-15Ra plus rhIL-15 to generate the NK-DLI. T cell add back to the CD34 selected graft ranged from 1-2 x 10e4 T cells/kg. NK-DLI was administered at days 21 and 49 (+/- 3 days) post-transplant. Patients received a myeloablative preparative regimen (TBI 1200 cGy and cyclophosphamide 60 mg/kg x 2 days). Recipients of unrelated donor products received GVHD prophylaxis with tacrolimus and were dose escalated separately. The starting dose for NK-DLI was 1 x $10^5$ NK cells/kg for unrelated donor recipients and 1 x $10^6$ NK cells/kg for related donor recipients.
**Results:** Six patients with high-risk ALL underwent transplant (Table). The median time to neutrophil and platelet engraftment was 9 and 12 days respectively. Median whole blood and CD3 donor chimerism at day 28 was 91% (range, 49-100%) and 52% (range, 0-97%). Despite achieving primary engraftment, one patient had absence of donor lymphoid engraftment and underwent a second RIC T-replete HCT to treat secondary rejection. Another subject received DLI to treat mixed chimerism. Although persistence or engraftment of infused NK-DLI cannot be definitely determined, in 5 of 6 recipients, the absolute NK value post-infusion was a median of 2.8 fold higher (range 1.7-4.3) than the pre-infusion value. Two subjects had grade 1 GVHD. All subjects received the second NK infusion off any immunosuppression. With limited follow up, all patients remain disease free (2-12 months post-HCT).
**Conclusions:** Infusion of ex-vivo, aAPC expanded NK-DLI is feasible and can be safely performed following myeloablative allogeneic HCT in patients with high-risk leukemia. Accrual and follow-up are ongoing.

| Pt# | Age (yrs)/ Sex | Donor | Disease status | CD34 dose/kg (x$10^6$) | NK dose/kg | Day of NK cell infusion | NK associated toxicity |
|---|---|---|---|---|---|---|---|
| 1 | 23/M | MRD | CR3 | 4.65 | 1 x $10^6$ | 23; 75 | Grade 1 GVHD |
| 2 | 24/M | MUD | CR3 | 5.14 | 1 x $10^5$ | 24; 87 | Grade 1 GVHD |
| 3 | 25/F | MRD | CR3 | 8.69 | 1 x $10^6$ | 23 | None |
| 4 | 18/M | MRD | CR2 | 4.88 | 1 x $10^6$ | 22; 54 | None |
| 5 | 18/M | MUD | CR4 | 9.45 | 1 x $10^5$ | 24 | Too early |
| 6 | 6/M | MUD | CR3 | 10 | 1 x $10^5$ | 26 | Too early |

*Disease status: CR=complete remission #*

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### A Change in Donor Medical Suitability Criteria Resulted in Decreased Rates of Donor Attrition at CT Stage in a Registry Study

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**Introduction:** Unrelated donor (UD) attrition is a serious problem impacting patients awaiting a transplant. In 2011 we presented results from a study of 7541 UD showing that donor attrition at CT was 38.2% and significantly worse in women, ethnic minorities, non-blood donors and those being on the register longer.

Since then 3 significant changes have been made: the joining age was reduced to 16-30 (previously 18-40), the maximum BMI allowed for PBSC donors was increased from 35 to 40 and an improved tracing system for uncontactable donors was introduced.

The objective of this work was to assess the impact of these changes on the proportion of donors involved in the cancellation of requests.
**Methods:** All CT requests made from Anthony Nolan in 2013 were reviewed, and outcomes documented. For each request, donor characteristics were documented.
**Results:** In 2013, 4207 requests were performed; 56.8% were completed, while 37.7% were cancelled for donor reasons. The univariate analysis showed that longer duration on the register ($p<0.001$), not being a blood donor ($p<0.001$) and African, African-Caribbean and Asian ethnicities ($p<0.001$) were associated with higher attrition rates.

Compared to our previous study we found similar attrition rates overall (38.2% to 37.7%; $p=0.6$). However, there was a reduction in donor cancellations for medical reasons (30% to 14.8%; $p < 0.001$). Conversely, we found that the attrition rates due to emigration or travel had increased (7.9% to 13%; $p<0.001$).

**Conclusion:** In conclusion, although a similar rate of attrition was seen in donors overall, the reasons were different from our previous study. Two of the changes instituted are likely to have contributed (lowering joining age and increasing BMI). Further work must be done on understanding other factors associated with attrition, and collaborating with other international registries to permit access to donors who have moved to other countries.

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### Differential Impact of Dose Escalated Busulfan on Allogeneic Transplant for High, Intermediate and Low Risk Disease

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Disease relapse, graft vs host disease and infection remain the major barriers to successful allogeneic stem cell transplantation. We previously presented data on the use of escalated AUC based dosing of a continuous infusion (CI) of IV busulfan over four days (Walko, BBMT, S218, 2012). In that report, we described use of a test dose and day 1 and 4 PK values to determine the dose delivered, and identified dose limiting toxicities as rash and mucositis at an AUC of 8300 um-min/day and identified an AUC MTD of approximately 6912 uM-min/day x 4 days; a 40% increase over a standard AUC dose of 4800 uM-min/day. Here we report additional analyses to identify patients (pts) likely to benefit from this higher dose of continuous infusion busulfan.

**Methods:** Patients with advanced hematologic malignancies and adequate organ function who were appropriate for a MUD or MRD allogeneic transplant were enrolled on an IRB approved trial of a test dose of busulfan (.8 mg/kg x 1) followed by escalated dose busulfan (4800-8300 uM-min/d) given as a 90 hour continuous infusion along with fludarabine at 30 mg/m$^2$/d x 5. Pts received tacrolimus and either alemtuzamab (30), ATG + MTX (19) or MTX alone (6) as GVH prophylaxis with standard anti-infective and supportive care.

**Results:** 55 pts (median age 41, range 20-55) with myeloid (38), lymphoid (8), or biphenotypic (1) leukemias, MDS or MF (1) or lymphomas (7) were enrolled. All 55 subjects were analyzed according to their being in the AUC low (group 1, 19 pts), middle (group 2, 19 pts), or high dose (group 3, 17 pts). 17 subjects had low, 20 had intermediate, and 18 had high-risk disease by CIBMTR criteria. For the entire group, univariate analysis identified age, recipient CMV status, and disease risk as significant factors for overall (OS) and relapse free survival (RFS). Co-morbidity scores, GVH occurrence or prophylaxis, donor/recipient sex and donor type (MUD or MRD) were not significant, nor was the non-relapse mortality rate different between the three AUC groups. Multivariable analysis identified CMV status as borderline significant (p=.07), and high vs low AUC dose (p=.053) and disease risk (p=.01) as significant for both OS and RFS. Outcomes were similar between AUC groups 2 and 3. Differences in OS and RFS were limited to the good and intermediate risk patients as outcomes for high-risk patients were poor for all AUC groups (0/17 RFS and 1/17 OS). When analyzing the 38 good and intermediate risk patients, the OS and RFS were 66% and 62.5% for combined AUC groups 2 and 3 compared to 31% (p=.02) for both OS and RFS in AUC group 1.

**Conclusions:** Targeted, PK based, CI busulfan that is approximately 40% higher than standard doses can result in apparent benefit for patients with CIBMTR low or intermediate risk disease. These doses were unable to demonstrate benefit in high-risk patients for whom other approaches such as immunotherapy, hypomethylating agents, or small molecule inhibitors may be needed.

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### Predictive Limitations of Hematopoietic Stem Cell Transplantation Associated Mortality: A Machine Learning in-Silico Analysis of the EBMT - Acute Leukemia Working Party Registry

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Several risk scores have been developed for the prediction of transplant related mortality (TRM) following allogeneic hematopoietic stem cell transplantation (HSCT). These have been validated; however, predictive performance is suboptimal. In addition to inherent uncertainty in such a complex medical procedure, methodological factors impeding prediction might be attributed to the statistical methodology, number and quality of features collected, or simply the population size. Using an *in-silico* approach (i.e. iterative computerized simulations), based on machine learning (ML) algorithms, we set to explore the factors limiting prediction.

ML is a subfield of computer science and artificial intelligence that deals with the construction and study of systems that can learn from data, rather than follow explicitly programmed instructions. Commonly applied in complex data scenarios, such as financial and technological settings, it may be suitable for outcome prediction of HSCT.

Study design involved two phases. The first, focused on development of several ML based prediction models of day